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WO 2005/056010 A1

(54) **Title:** PREVENTION AND/OR REDUCTION OF PHOTORECEPTOR DEGENERATION WITH RETINOIDS

(57) **Abstract:** The present invention provides a method for reducing and/or preventing degeneration of photoreceptors in the eye of a human caused by radiation in the visible range which comprises administering to said mammal a retinoid compound having RAR beta and/or RAR-delta-selective agonist activity, and more specifically Tazarotene.

PREVENTION AND/OR REDUCTION OF PHOTORECEPTOR DEGENERATION WITH RETINOIDS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to administering RAR_β and/or RAR_δ-selective retinoid agonists to a human to prevent and/or reduce photoreceptor damage caused by visible light, e.g. blue light.

2. Background of the Related Art

It has been observed that isotretinoin (13-cis retinoic acid or ACCUTANE®) can protect photoreceptors of rats and mice from light damage. (See Sparrow, PNAS, April 15, 2003, vol. 100, no. 8, 4353-4354. See also Seiving, et al, PNAS, February 13, 2001, vol. 98, no. 4, 1835-1840.) However, isotretinoin is well known to cause birth defects and is a non selective retinoid, i.e. it is not retinoid receptor subtype selective.

Tazarotene is a RAR_β and RAR_δ-selective retinoid agonist which has been used for treating psoriasis and/or acne. (See U.S. Patent 5,089,509.) Tazarotene and other related retinoids are disclosed for treating various other diseases and conditions which are responsive to treatment with retinoid compounds. (See U.S. Patent Nos. 5,750,693; 6,090,826 and 6,344,463.) Also, it has recently been disclosed that tazarotene and certain other retinoid agonists are useful in preventing the proliferation of retinal pigment epithelium following surgery or trauma or resulting from ocular diseases associated with choroidal neovascularization, such as age-related macular degeneration and histoplasmosis syndrome. (See U.S. Patent Nos. 5,824,685; 6,075,032; 6,071,924; 6,372,753; 5,437,291 and 5,674,205.)

BRIEF SUMMARY OF THE INVENTION

This invention provides a method for reducing and/or preventing degeneration of photoreceptors in the eye of a mammal caused by radiation in the visible range e.g. blue light, which comprises administering to said mammal a retinoid compound having RAR_β and/or RAR_δ-selective agonist activity. In particular, the invention provides a method of treating diseases and conditions resulting from or caused by exposure to visible radiation, especially radiation in the blue band of the visible spectrum, e.g. radiation of about 480 nm. Such diseases or conditions include, but are not limited to non-exudative age related macular degeneration (ARMD), exudative age related macular degeneration (ARMD), choroidal neovascularization, diabetic retinopathy, central serous chorioretinopathy, cystoid macular edema, diabetic macular edema, myopic retinal degeneration, acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (MEWDS), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-Harada syndrome, punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, acute retinal pigment epitheliitis, acute macular neuroretinopathy, diabetic retinopathy, retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, Eales disease, sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, laser, photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, bone

marrow transplant retinopathy, proliferative vitreal retinopathy and epiretinal membranes,

ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associated with HIV infection, uveitic disease associated with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, myiasis, retinitis pigmentosa, systemic disorders with associated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, x-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, pseudoxanthoma elasticum, retinal detachment, macular hole, giant retinal tear, retinal disease associated with tumors, congenital hypertrophy of the retinal pigment epithelial (RPE), posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hematoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma and intraocular lymphoid tumors.

Preferably, the retinoid compound is selected from the group consisting of tazarotene, i.e. ethyl-6-[2-(4,4-dimethyl-thiochroman-6-yl)ethyl]nicotinate, tazarotenic acid and other lower alkyl esters of tazarotenic acid, e.g. C_2-C_6 alkyl esters of tazarotenic acid, such as methyl 6-[2-(4,4-dimethyl-thiochroman-6-yl)ethyl]nicotinate, i-propyl 6-[2-(4,4-dimethyl-thiochroman-6-yl)ethyl]nicotinate, n-butyl 6-[2-(4,4-dimethyl-thiochroman-6-yl)ethyl]nicotinate, etc.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Figure 1 shows the effect of the exposure of test rats to blue light, at a wavelength of 480 nm. In particular, this Figure shows that the photoreceptor layer of the test subjects is badly damaged.

Figure 2, in comparison to Figure 1, shows the protective effect to the photoreceptor layer of test rats dosed with retinoids or brimonidine.

Figure 3 shows the protective effect to the photoreceptor layer of the test rats dosed with an RAR agonist or an RXR agonist as measured by ERG.

Figure 4 shows the relative response of the measured ERG of the photoreceptor layer of the test rats dosed with retinoids or brimonidine.

Figure 5 shows the loss of protective effect of an RAR agonist when dosed in combination with an RAR antagonist.

DETAILED DESCRIPTION OF THE INVENTION

Tazarotene has been used for treating acne and psoriasis and other diseases that are known to be responsive to treatment with retinoids. Also, it has recently been disclosed that tazarotene and other retinoid agonists are useful in preventing the proliferation of retinal pigment epithelium following surgery or trauma or resulting in ocular diseases associated with choroidal neovascularization, such as age-related macular degeneration and histoplasmosis syndrome.

It has now been surprisingly found that tazarotene may be used to treat diseases and/or conditions of the eye caused by exposure to visible radiation, e.g. radiation in the blue band of the spectrum. While not wishing to be bound by theory, it is postulated that tazarotene is effective as a result of its ability to act as an RAR_β and/or RAR_γ-selective retinoid agonist. (The RAR_β and/or RAR_γ-selective retinoid, utilized in the method of the present invention will

preferably be incapable of agonist activity at any o the RXR receptors, and have a potency of RAR_α/RAR_β of greater than 15 and/or RAR_α/RAR_γ of greater than 30 as determined according to the cotransfection assay of Example 1 of U.S. Patent 6,075,032. More preferably, the retinoid utilized in the method of the present invention will have a potency of RAR_α/RAR_β of greater than 15 and RAR_α/RAR_γ of greater than 30. See Table 1 of U.S. Patent 6,075,032.)

A preferred embodiment of the present invention is the use of tazarotene for treating age-related macular degeneration, diabetic retinopathy and/or retinitis pigmentosa resulting from such radiation by contacting the eye of a person suffering from such conditions with a therapeutically effective amount of tazarotene. A therapeutically effective amount is an amount of the active agent that is effective in achieving the desired therapeutic effect. The therapeutically effective amount depends on the administration regimen, the condition of the treated individual, etc. as known per se.

To achieve a therapeutic effect of the RAR_β and/or RAR_γ-selective retinoids in the method of the present invention, the retinoid may be administered systemically, e.g. orally, or topically, e.g. by eye drop or site-selective injection into the eye, depending on the condition to be treated, the need for site-selective treatment, quantity of retinoid to be administered, and other considerations.

The invention further relates to the use of tazarotene or other RAR_β and/or RARγ-selective retinoids for the preparation of an ophthalmologic compositions for the treatment of ARMD, diabetic retinopathy and/or retinitis pigmentosa. That is, tazarotene is mixed with a conventional ophthalmologically compatible vehicle, for example, aqueous solutions such as physiological salines, oil solutions, or ointments. The vehicle may contain ophthalmologically compatible preservatives such as benzalkonium chloride, surfactants such as polysorbate 80, liposomes, or polymers such as methylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid, which may be used for increasing the viscosity.

As used herein, the term "a therapeutically effective amount" of tazarotene or other RAR_β or an RAR_γ-selective retinoid agonist is an amount calculated to achieve and maintain a therapeutic level in the eye, if introduced directly into the vitreous cavity or periocular space, or in the bloodstream, if administered peripherally, over the period of time desired in a human or animal such as to be effective in treating the adverse condition. The therapeutic amount will vary with the potency of each RAR_β and/or RAR_γ-selective retinoid agonist, the amount required for the desired therapeutic or other effect, the rate of elimination or breakdown of the substance by the body once it has entered the vitreous cavity or bloodstream, and the amount of the RAR agonist in the formulation. In accordance with conventional prudent formulating practices, a dosage near the lower end of the useful range of a particular agent is usually employed initially, and the dosage is increased or decreased as indicated from the observed response, as in the routine procedure of the physician.

For administration directly into the vitreous cavity of the eye, an amount in the range between about 50 and 150 μg may be administered one or more times to achieve the desired therapeutic result. Alternatively, a combination of intravitreal and subconjunctival injection of the retinoid, either simultaneously or at spaced intervals, can be used to administer the retinoid. For intravitreal injection, it is preferred that the RAR agonist be injected into the anterior vitreous cavity using topical or retrobulbar anesthesia. In an alternative embodiment, the RAR agonist is introduced intravitreally using a drug delivery vehicle. For instance, the RAR agonist can be dissolved in a biologically inert fluid that is also useful as a mechanical tamponade to help keep the retina in place, preferably an oil such as silicone oil in which the retinoid is soluble. However, for RAR agonists having partial miscibility, a liquid other than an oil can be used.

It has been discovered that the therapeutic effects of the retinoids of this invention may be delayed in onset and reversible. Therefore, it may be advantageous to administer the retinoids utilizing a method of a slow release, for instance by intravitreal injection of the dose of retinoid encapsulated in a

microvesicle, such as a liposome, from which the dose is released over the course of several days, preferably between about 3 to 20 days. Alternatively, the drug can be formulated for slow release, such as incorporation into a slow release polymer from which the dosage of drug is slowly released over the course of several days, for example from 2 to 30 days. The slow release formulation may be placed in the eye by intravitreal, subconjunctival, periocular, intrascleral or subretinal injection. The retinoid may be incorporated into a bioerodible polymer such as a polylactic acid-glycolic acid copolymer, e.g. Oculex®.

The ophthalmologic compositions of this invention may be administered in a number of ways. By one mode of administration, said ophthalmologic composition is applied topically onto the eye. For topical application, said ophthalmologic composition may be formulated with a vehicle that is compatible with the eye and preferably such that facilitates penetration of tazarotene into the eye. For such mode of application, said active agent may be formulated in the form of eyedrops (in which the tazarotene or other RAR_β and/or RAR_γ-selective retinoid agonist is dissolved in a physiological solution), in the form of ointments, in the form of a liposome solution, etc.

It is contemplated that the dosing levels of tazarotene as used in the eye drops of the present invention would be adjusted as necessitated by lack of response, speed of response needed, strength of tazarotene solution, etc.

The method of the present invention may be practiced alone or in conjunction with other therapy.

The invention is further illustrated by the following examples which are illustrative of specific modes of practicing the invention and are not intended as limiting the scope of the appended claims.

Adult male abino Sprague-Dawley rats (weight 400 ± 30 g) were used for the following examples. After 18 hours of dark adaptation, animals were housed in specially designed acrylic cages and exposed to high intensity (12000 LUX) of blue fluorescent light (480 nm) for 8 hours. The light intensity was measured with a digital light meter. Each animal was housed separately. The room was maintained at 73 ° F throughout the experiment.

Animals were orally dosed with the appropriate retinoid or positive control, i.e. brimonidine, for 5 days with the last dose administered 2 hours before blue-light exposure. After the light exposure, the animals were kept in the dark room and recovered for an additional 5 days. Retinal function was evaluated with flash ERG analysis. Retinal structure was assessed by histology.

Example 1

As shown in Figure 1, the photoreceptor layer is badly damaged by exposure to blue light in this experiment where the animals are not dosed with a retinoid or other neuroprotective agent.

Example 2

The following retinoids were evaluated for preventing damage to the photoreceptor layer of rats subjected to exposure to blue light.

Retinoid compound tested/receptor selectivity/dose.

Tazarotene/(RAR agonist)/ 3 mg/kg/day

Compound A/ (RXR agonist)/ 10 mg/kg/day

Compound B/ (RXR antagonist)/ 50 mg/kg/day

Compound C/ (RAR antagonist)/ 3 mg/kg/day

Compound A
3,7-Dimethyl-6(S),7(S)-methano-7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl]-2E, 4E-heptadienoic acid

Compound B
(2E,4E,6E)-7-(3,5-Diisopropyl-2-propoxy-phenyl)-6-fluoro-3-methyl-nona-2,4,6-trienoic acid
Compound C
4-2(6-(2,2-Dimethyl-(1H)-4-(4-ethylphenyl)-1-benzothiopyran))ethynyl]benzoic acid

As shown in Figure 2, the thickness of the photoreceptor layer for the animals dosed with brimonidine, a well known neuroprotective agent is much

greater than the thickness of the photoreceptor layers of the animals dosed with the vehicle alone, or the RAR antagonist or the RXR antagonist. The thickness or the photoreceptor layer for the RXR agonist is greater than the photoreceptor layers of the animals dosed with the RAR or RXR antagonists but, the photoreceptor layer of the animal dosed with the RAR agonist is the best of the retinoids tested and almost equivalent in effect to brimonidine. (The RAR agonist, tazarotene, is an RAR_β and RARδ-selective retinioid. The RXR agonist also has some RAR agonist activity.)

Also, as shown in Figure 3, which is a plot of the ERG wave verses time, the RAR agonist and the RXR agonist show a protective effect to the photoreceptor layer when measured by ERG.

Figure 4, shows in a bar chart the relative response of the ERG wave for the above animals after exposure to blue light.

Example 3

In this Example, the above experiment is repeated with the RAR antagonist, which has antagonist activity at the α, β and δ retinoid receptor subtype dosed in combination with the RAR agonist and the RXR agonist.

Figure 5 shows that the RAR antagonist severely diminishes the effectiveness of both the RAR agonist and the RXR agonists, therefore demonstrating that the effectiveness of the RXR antagonist is a result of its RAR agonist activity and not its RXR antagonist activity.

Example 4

The following retinoid compounds were tested in the above method with the results reported as shown.

Retinoid Compound/Receptor Selectivity	Protective Activity

Tazarotene/ ($RAR_{\beta, \gamma}$ agonist)	***
Compound A/ ($RXR_{\alpha, \beta, \gamma}$ agonist with RAR activity)	**
Compound C/ ($RAR_{\alpha, \beta, \gamma}$ antagonist)	X
Compound B/ (RXR_{α}, β, γ antagonist)	X
Compound D/(RAR_{α} antagonist)	X
Compound E/(RAR_{α} agonist)	**
Compound F/($RXR_{\alpha, \beta, \gamma}$ agonist)	X

* means a protective effect of the photoreceptor layer to damage from blue light radiation. Greater effectiveness is shown by increasing number of *'s.

X means no such protective effect.

Compound D
2-Fluoro-4-[6'-(2",2"-dimethyl-4"-tolyl chromanyl)-8'-bromo]carbamoyl benzoic acid

Compound E
4-[(4-Chloro-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-amino]-2,6-difluoro-benzoic acid

Compound F
3-Methyl-7-propyl-6(S),7(S)-methano-7[1,1,4,4-tetrametyl-1,2,3,4-tetrahydro-7-yl]-2(E),4(E)- heptadienoic acid

Example 5

In an example of treatment according to the preferred embodiment described above, a male patient aged 64 with blue eyes is diagnosed with age-related macular degeneration of about ten years' duration. Numerous druscen was documented in both eyes. Photographs of the fundus are obtained. Treatment with tazarotene according to the preferred method of use described herein is initiated in the left eye.

After two years of treatment, the treated eye shows no changes in visual acuity from that measured at the start of treatment. There are also no changes in the fundus, such as increases in the number or extent of the druscen, compared with the photographs obtained before the start of treatment. Thus, treatment with tazarotene according to the methods of the present invention prevents any additional effects from macular degeneration from occurring in the treated eye. This is significant because, as described above, the normal course of macular degeneration leads to a continuous, on-going loss of vision over time.

The above disclosure sets forth an embodiment of the present invention. Other arrangements or embodiments, not precisely set forth, could be practiced under the teachings of the present invention.

While the present invention has been described in the context of treating age-related macular degeneration, tazarotene may also be used for treating retininitis pigmentosa, diabetic retinopathy, ischemic retinopathy damage caused by surgery, e.g. laser or mechanical, and photodynamic therapy and any of the other diseases and/or conditions disclosed above.

Moreover, while the present invention is described for treating retinitis pigmentosa with tazarotene, the corresponding acid, i.e. tazarotenic acid may also be used, as well as other C_1 to C_6 lower alkyl esters of tazarotenic acid, e.g. the methyl and isopropyl esters of tazarotenic acid.

The above disclosure sets forth certain preferred embodiments of the present invention. Other arrangements or embodiments, not precisely set forth, could be practiced under the teachings of the present invention.

We claim:

1. A method for reducing and/or preventing degeneration of photoreceptors in the eye of a human caused by radiation in the visible range which comprises administering to said mammal a retinoid compound having RAR_β and/or RAR_δ-selective agonist activity.

2. The method of claim 1 wherein said radiation is blue light radiation.

3. The method of claim 1 wherein said retinoid compound is tazarotenic acid or a lower alkyl ester or salt thereof.

4. The method of claim 3 wherein said compound is tazarotenic acid or tazarotene.

5. The method of claim 4 wherein said compound is tazarotene.

6. A method of treating diseases or conditions in a mammal resulting from or caused by exposure to visible radiation which comprises administering to said mammal a retinoid compound having RAR_β and/or RAR_δ-selective agonist activity.

7. The method of claim 6 wherein said radiation is blue light radiation.

8. The method of claim 6 wherein said retinoid compound is tazarotenic acid or a lower alkyl ester or salt thereof.

9. The method of claim 6 wherein said compound is tazarotenic acid or tazarotene.

10. The method of claim 6 wherein said compound is tazarotene.

11. The method of claim 1 wherein said mammal has a condition selected from the group consisting of non-exudative age related macular degeneration (ARMD), exudative age related macular degeneration (ARMD), choroidal neovascularization, diabetic retinopathy, central serous chorioretinopathy,

cystoid macular edema, diabetic macular edema, myopic retinal degeneration, acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (MEWDS), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-Harada syndrome, punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, acute retinal pigment epitheliitis, acute macular neuroretinopathy, diabetic retinopathy, retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, Eales disease, sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, laser, photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, bone marrow transplant retinopathy, proliferative vitreal retinopathy and epiretinal membranes, ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associated with HIV infection, uveitic disease associated with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, myiasis, retinitis pigmentosa, systemic disorders with associated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, x-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, pseudoxanthoma elasticum, retinal detachment, macular hole, giant retinal tear, retinal disease

associated with tumors, congenital hypertrophy of the retinal pigment epithelial (RPE), posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hematoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma and intraocular lymphoid tumors.

12. The method of claim 11 wherein said condition is age related macular degeneration.

13. The method of claim 11 wherein said condition is retinitis pigmentosa.

14. The method of claim 11 wherein said condition is diabetic retinopathy.

15. The method of claim 11 wherein said condition is surgical trauma.

16. The method of claim 11 wherein said condition is laser induced damage.

Photoreceptor significantly damaged after light-induced damage

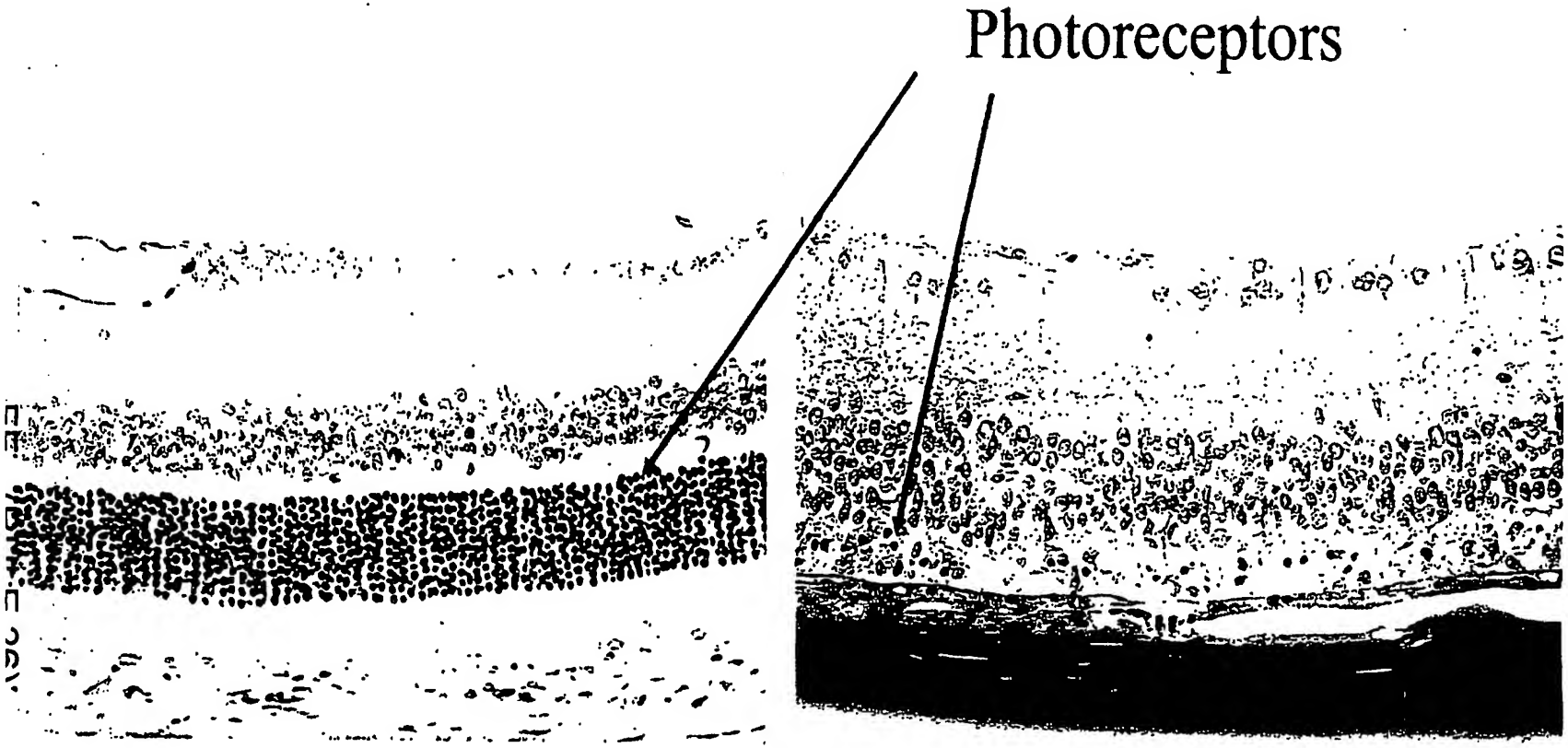

FIG. 1.

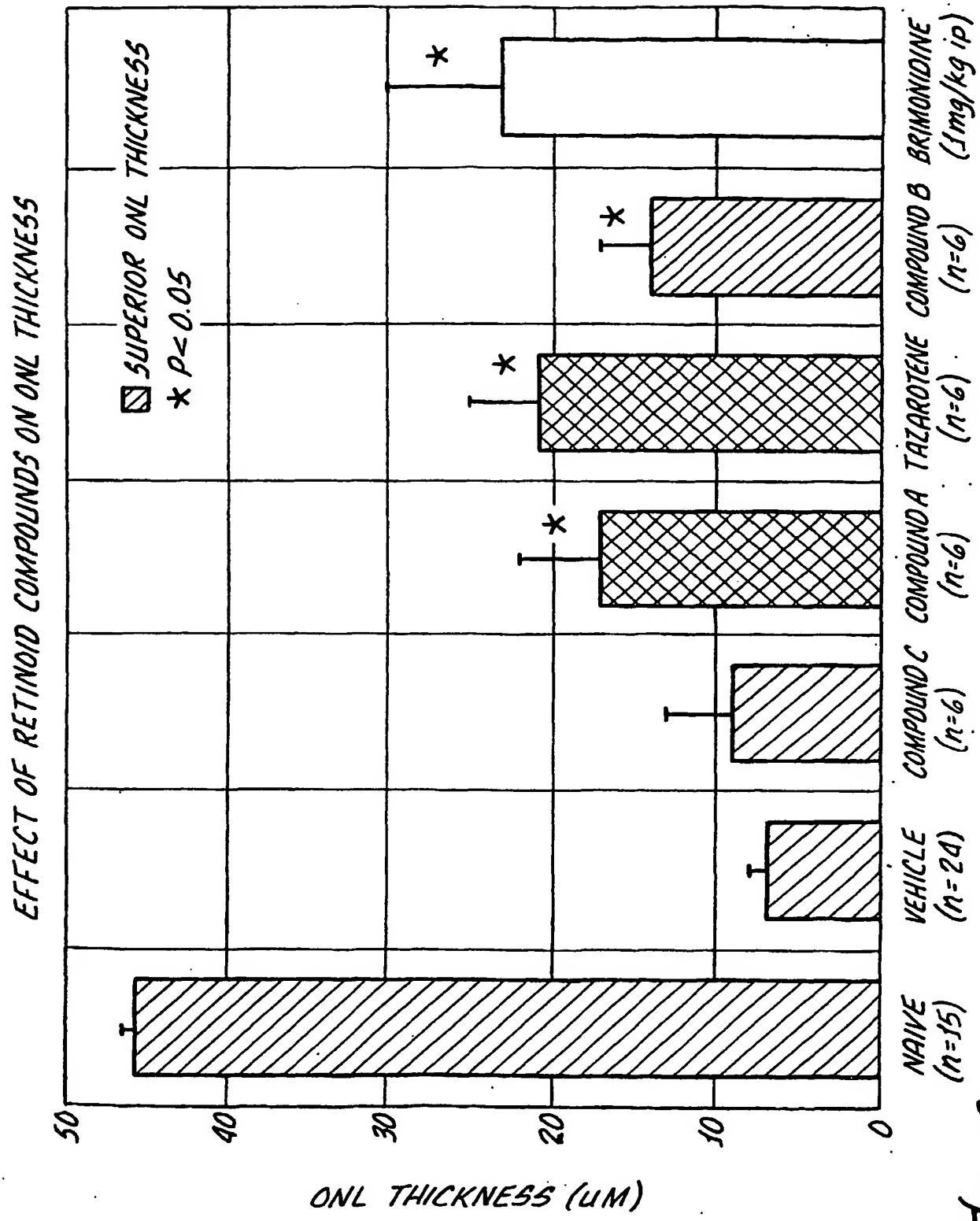

FIG. 2.

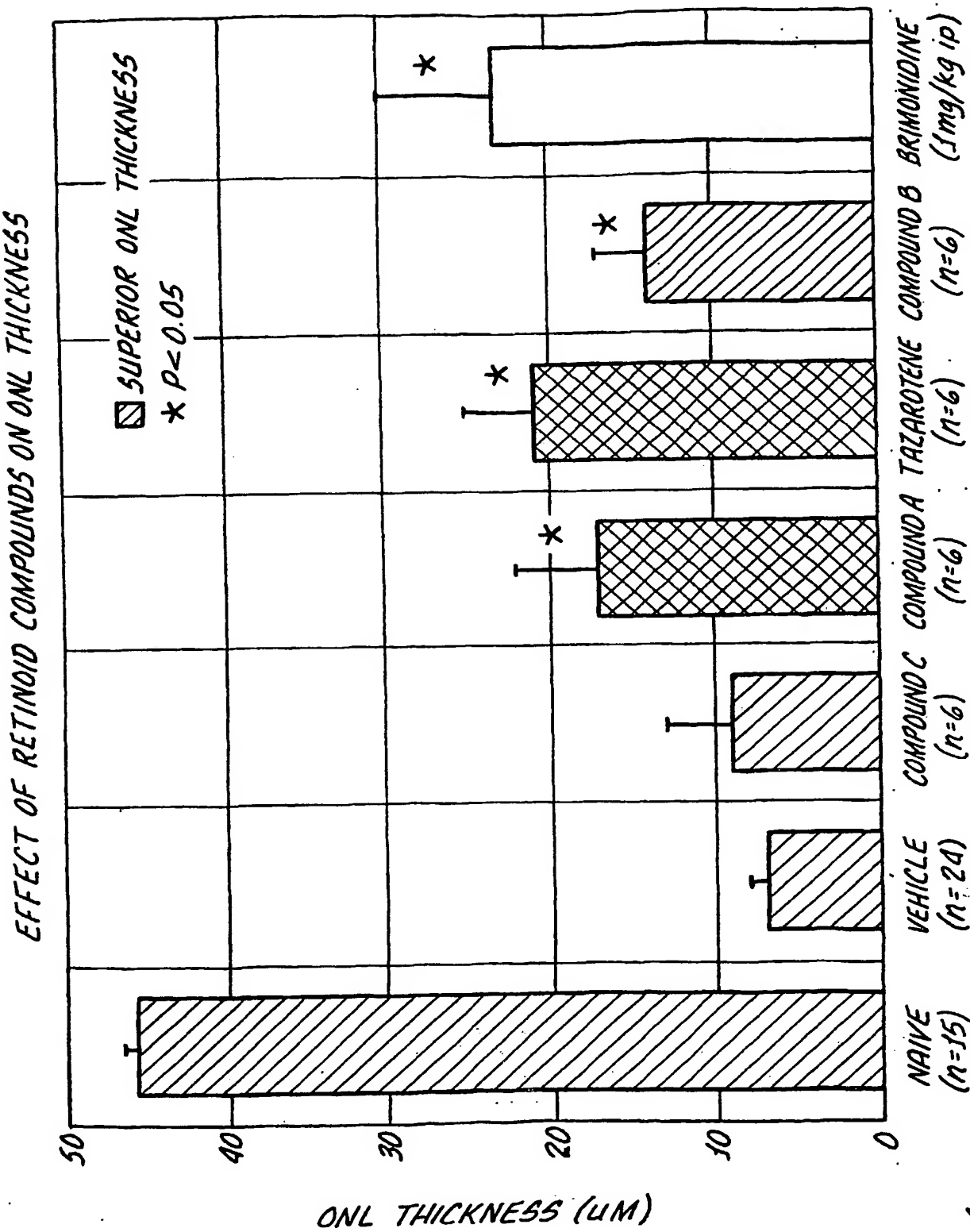

FIG. 2.

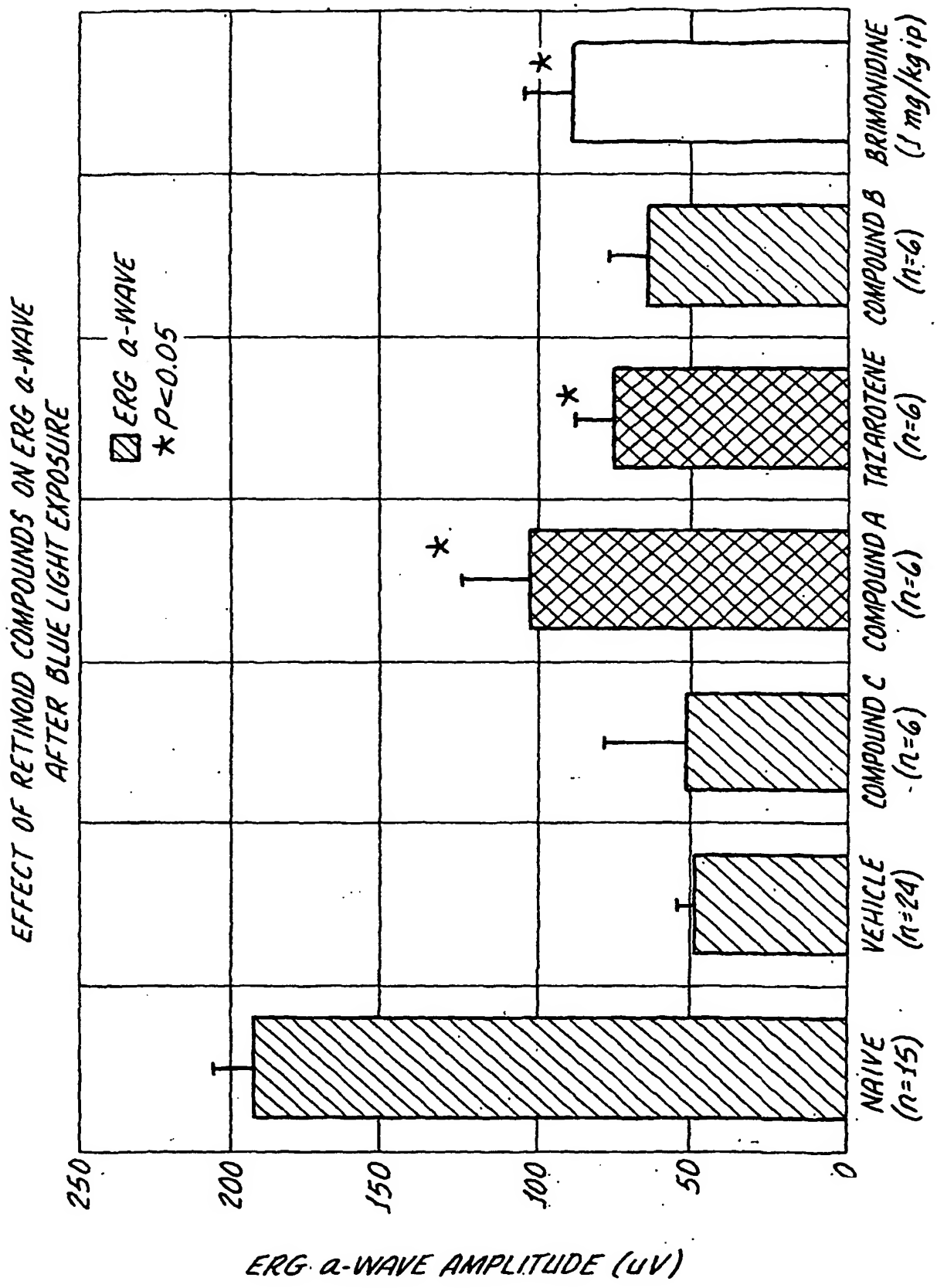

FIG. 4.

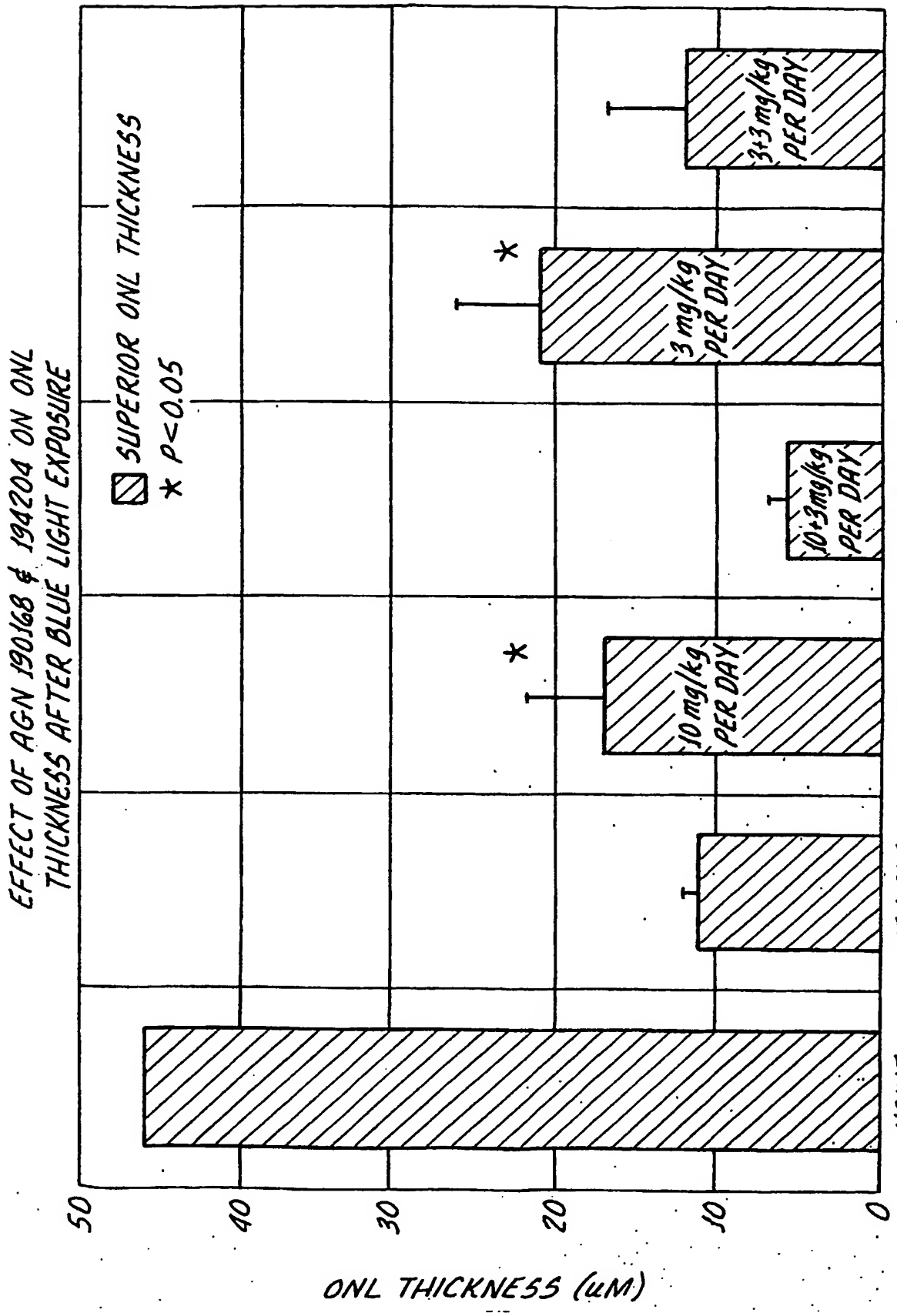

FIG. 5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/039987

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4436 A61K31/203 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, CHEM ABS Data, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 824 685 A (CAMPOCHIARO ET AL) 20 October 1998 (1998-10-20) abstract column 3, line 48 - column 6, line 49; examples 8-11; tables 6-10	1-5,11, 12,15
X	WO 96/11686 A (ALLERGAN, INC) 25 April 1996 (1996-04-25) abstract page 6, paragraph 3 - page 7, paragraph 5; claims 1,4,15; example 6	1-11
X	US 5 919 970 A (SONG ET AL) 6 July 1999 (1999-07-06) abstract column 4, line 62 - column 5, line 4; table 2	1,11

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[X] Further documents are listed in the continuation of box C

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2005	01/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	SCHOENFELD C-L: "HEMMUNG DER PROLIFERATION RETINALEN PIGMENTEPITHELS IN VITRO VITAMIN A-PHARMAKODYNAMIK I INHIBITION OF PROLIFERATION OF RETINAL PIGMENT EPITHELIUM IN VITRO: VITAMIN A PHARMACODYNAMICS I" OPHTHALMOLOGE, SPRINGER, BERLIN,, DE, vol. 97, no. 1, 2000, pages 5-11, XP008046778 ISSN: 0941-293X the whole document	1,11
E	WO 2005/011741 A (ALLERGAN, INC; HUGHES, PATRICK, M; OLEJNIK, CREST) 10 February 2005 (2005-02-10) abstract page 3, line 30 - page 4, line 29 page 6, line 15 - page 8, line 17 page 10, line 2 - page 11, line 10; claims 1,7,8,13,17; table 1	1-16
A	GRONDONA J M ET AL: "Retinal dysplasia and degeneration in RARbeta2/RARgamma2 compound mutant mice." DEVELOPMENT (CAMBRIDGE, ENGLAND) JUL 1996, vol. 122, no. 7, July 1996 (1996-07), pages 2173-2188, XP008046801 ISSN: 0950-1991 the whole document	1-16
A	MORI M ET AL: "Systematic immunolocalization of retinoid receptors in developing and adult mouse eyes" INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE 2001 UNITED STATES, vol. 42, no. 6, 2001, pages 1312-1318, XP008046773 ISSN: 0146-0404 the whole document	1-16
A	WO 99/07418 A (ALLERGAN SALES, INC) 18 February 1999 (1999-02-18) the whole document	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/039987

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos..
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/039987

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